Combined Effects of Routine Blood Pressure Lowering and Intensive Glucose Control on Macrovascular and Microvascular Outcomes in Patients With Type 2 Diabetes

New results from the ADVANCE trial

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OBJECTIVE — To assess the magnitude and independence of the effects of routine blood pressure lowering and intensive glucose control on clinical outcomes in patients with long-standing type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a multicenter, factorial randomized trial of perindopril-indapamide versus placebo (double-blind comparison) and intensive glucose control with a gliclazide MR–based regimen (target A1C ≤6.5%) versus standard glucose control (open comparison) in 11,140 participants with type 2 diabetes who participated in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial. Annual event rates and risks of major macrovascular and microvascular events considered jointly and separately, renal events, and death during an average 4.3 years of follow-up were assessed, using Cox proportional hazards models.

RESULTS — There was no interaction between the effects of routine blood pressure lowering and intensive glucose control for any of the prespecified clinical outcomes (all $P > 0.1$): the separate effects of the two interventions for the renal outcomes and death appeared to be additive on the log scale. Compared with neither intervention, combination treatment reduced the risk of new or worsening nephropathy by 33% (95% CI 12–50%, $P = 0.005$), new onset of macroalbuminuria by 54% (35–68%, $P < 0.0001$), and new onset of microalbuminuria by 26% (17–34%). Combination treatment was associated with an 18% reduction in the risk of all-cause death (1–32%, $P = 0.04$).

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CONCLUSIONS — The effects of routine blood pressure lowering and intensive glucose control were independent of one another. When combined, they produced additional reductions in clinically relevant outcomes.

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Type 2 diabetes affects >240 million people worldwide and significantly contributes to the global burden of vascular disease, of which both blood pressure and glucose are important determinants (1). Large-scale, randomized controlled trials have clearly documented the benefits of blood pressure–lowering treatment on the risk of macrovascular and microvascular complications and on survival among patients with type 2 diabetes (2–4). Intensive glucose control has been shown to reduce the risk of microvascular complications (5–8), although it did not improve patient survival or alter the course of macrovascular complications in the first 3–10 years (7–10). Current guidelines recommend a multifactorial approach with simultaneous targeting of elevated blood pressure and glucose levels in individuals with type 2 diabetes (11–13). However, it is not known whether combining blood pressure lowering and glucose control can reduce the risk of vascular complications to a greater extent than either treatment alone.

Results from the UK Prospective Diabetes Study (UKPDS) have suggested that the effects of blood pressure– and glucose-lowering interventions might be additive (14). In post hoc analyses, the associations between vascular outcomes and systolic blood pressure or A1C levels achieved during follow-up were independent, and there was a trend toward the greatest benefit with the combination of intensive blood pressure– and glucose-lowering interventions (14). However, because only a small subset of hyperten-

sive subjects received both interventions, the UKPDS had insufficient power to determine conclusively whether the effects of the treatments were additive in this group or in the broader population with type 2 diabetes. Moreover, the reported excess mortality in the intensive glucose control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study compared with that for those randomized to standard glucose control has raised concerns about whether intensive glucose lowering could modify or even negate the benefits of blood pressure lowering in patients with type 2 diabetes (9).

Recently the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, a large-scale, double-blind, randomized factorial trial among 11,140 people with type 2 diabetes, demonstrated the separate vascular benefits of routine blood pressure lowering with a fixed combination of perindopril and indapamide after 4.3 years of follow-up and of intensive glucose control, based on gliclazide MR, after 5 years of follow-up (4,8). In this report, we present new analyses that explore the extent to which blood pressure–lowering treatment and intensive glucose control provide independent and additive benefits with respect to vascular outcomes in patients with type 2 diabetes after 4.3 years of follow-up.

RESEARCH DESIGN AND METHODS

— ADVANCE was a factorial randomized controlled trial evaluating the effects of blood pressure lowering and intensive blood glucose control on vascular outcomes. Detailed descriptions of the study methods have been published previously (4,8,15). In brief, a total of 11,140 individuals with type 2 diabetes aged ≥55 years, with a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease, were enrolled from 215 centers in 20 countries. There were no A1C or blood pressure inclusion criteria. Approval for the trial was obtained from each center's institutional review board, and all participants provided written informed consent. After a 6-week active run-in period with fixed-combination perindopril and indapamide (2 mg/0.625 mg), during which usual glucose control was continued, participants were randomly assigned, in a factorial design, to continued perindopril-indapamide (2 mg/0.625 mg for the first 3 months then 4 mg/1.25 mg thereafter) or matching placebo and to ei-

ther an intensive glucose control strategy aiming for an A1C of ≤6.5% or a standard glucose control strategy (target A1C levels defined by local guidelines) using a central, computer-based randomization service. Participants randomly assigned to intensive glucose control were given gliclazide MR (30–120 mg daily) and other glucose-lowering drugs as required by their primary physicians (8). Participants randomly assigned to the standard control who were using gliclazide MR at study entry were required to substitute this with another sulfonylurea, if continued therapy was required (8).

Outcomes and follow-up

The primary outcomes were a composite of macrovascular (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) and microvascular (new or worsening nephropathy or retinopathy) events, considered jointly and separately (4,8). The secondary outcomes examined were death from all causes, cardiovascular death, major coronary events (death due to coronary heart disease [including sudden death] or nonfatal myocardial infarction), major cerebrovascular events (death due to cerebrovascular disease or nonfatal stroke), new or worsening nephropathy (requirement for renal replacement therapy, death from renal disease, development of macroalbuminuria, or a doubling of serum creatinine to a level of at least 200 μmol/l), new onset of microalbuminuria (urinary albumin-to-creatinine ratio 30–300 μg/mg) and total renal events (defined post hoc as the composite of new or worsening nephropathy or new onset of microalbuminuria), and new or worsening retinopathy. Primary outcomes and all deaths were reviewed and validated by an independent end point adjudication committee blinded to treatment allocation (4,8). For the purposes of this study, the joint effects of randomized treatments were studied after 4.3 years of follow up, that is, at completion of the blood pressure intervention, although the glucose-lowering intervention was completed after an average of 5 years.

Statistical analysis

Differences between randomized groups in blood pressure and A1C during follow-up were estimated using linear mixed models. Annual event rates were calculated with the person-years method. Combined treatment effects on study end points were estimated from unadjusted Cox proportional hazard models, using

survival time to the first relevant end point in any individual patient, according to the principle of intention to treat. Only the first event of the relevant outcome type was included in each analysis. Participants were censored at their date of death, date of last visit (for those still alive at the end of follow-up), or date when last known to be alive (for those with unknown vital status). For each outcome, interactions between treatment effects were tested by adding interaction terms to the relevant Cox models and comparing the likelihood statistics for the models with and without interaction; this will thus be termed a test for an additive interaction here. However, because Cox models work on the logarithmic scale, the null hypothesis being tested is that the joint effect of the two treatments is the product of their individual effects, with all effects measured through hazard ratios (HRs) (16). All *P* values were calculated from two-tailed tests of statistical significance with a type I error rate of 5%. All analyses were performed using SAS (version 9.1).

RESULTS

Baseline characteristics

The four treatment groups were well balanced for a range of baseline characteristics (Table 1). In all four groups, 32% of participants had a history of major macrovascular disease and 10% had a history of major microvascular disease. Mean duration of diabetes was 8 years, and mean entry A1C and blood pressure were 7.5% and 145/81 mmHg, respectively (Table 1).

Characteristics during follow-up

At the end of 4.3 years of follow-up, use of concomitant treatment was similar among the four treatment groups (supplementary Table, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-0959/DC1). Over the duration of 4.3 years, blood pressure was reduced by an average ± SEM of 7.1 ± 0.3 mmHg systolic and 2.9 ± 0.2 mmHg diastolic blood pressure in patients assigned to joint treatment compared with those assigned to neither treatment (*P* < 0.001). Similarly, A1C was reduced by 0.61 ± 0.02% after 4.3 years follow-up in patients assigned to joint treatment compared with those assigned to neither treatment (*P* < 0.001).

Table 1—*Characteristics of randomized participants at baseline*

Characteristic	Intensive glucose and perindopril-indapamide	Standard glucose and perindopril-indapamide	Intensive glucose and placebo	Standard glucose and placebo
n	2,783	2,786	2,788	2,783
Age (years)	65.8 ± 6.3	65.8 ± 6.4	65.7 ± 6.5	65.8 ± 6.4
Female sex	1,198 (43.0)	1,168 (41.9)	1,181 (42.4)	1,188 (42.7)
Age when diabetes first diagnosed (years)	57.8 ± 8.5	57.9 ± 8.9	57.8 ± 8.7	57.8 ± 8.8
Diabetes duration (years)	8.0 ± 6.4	8.0 ± 6.4	7.8 ± 6.3	8.0 ± 6.3
Prior vascular disease				
History of major macrovascular disease	896 (32.2)	902 (32.4)	898 (32.2)	894 (32.1)
History of myocardial infarction	339 (12.2)	339 (12.2)	329 (11.8)	327 (11.7)
History of stroke	254 (9.1)	248 (8.9)	261 (9.4)	259 (9.3)
History of major microvascular disease	281 (10.1)	287 (10.3)	288 (10.3)	296 (10.6)
History of macroalbuminuria	94 (3.5)	103 (3.9)	93 (3.5)	111 (4.2)
History of microvascular eye disease	195 (7.0)	194 (7.0)	206 (7.4)	198 (7.1)
History of microalbuminuria	726 (27.4)	715 (26.9)	711 (26.7)	710 (26.7)
Blood glucose control				
A1C concentration (%)	7.5 ± 1.6	7.6 ± 1.6	7.5 ± 1.6	7.5 ± 1.5
Fasting blood glucose (mmol/l)	8.6 ± 2.8	8.5 ± 2.8	8.5 ± 2.7	8.4 ± 2.8
Other major risk factors				
Systolic blood pressure (mmHg)	145.3 ± 22.1	144.8 ± 21.6	144.6 ± 21.3	145.3 ± 21.2
Diastolic blood pressure (mmHg)	80.9 ± 11.1	80.5 ± 11.0	80.6 ± 11.0	80.5 ± 10.7
Currently treated hypertension	1,909 (68.6)	1,893 (67.9)	1,907 (68.4)	1,946 (69.9)
Serum total cholesterol (mmol/l)	5.2 ± 1.2	5.2 ± 1.2	5.2 ± 1.2	5.2 ± 1.2
Serum LDL cholesterol (mmol/l)	3.1 ± 1.0	3.1 ± 1.0	3.1 ± 1.0	3.1 ± 1.0
Serum HDL cholesterol (mmol/l)	1.3 ± 0.3	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.3
Serum triglycerides (mmol/l)	1.6 (1.2–2.3)	1.6 (1.2–2.3)	1.6 (1.2–2.4)	1.7 (1.2–2.3)
Urinary albumin-to-creatinine ratio (μg/mg)	15 (7–40)	15 (7–40)	15 (7–39)	14 (7–40)
BMI (kg/m²)	28.4 ± 5.1	28.3 ± 5.3	28.4 ± 5.2	28.3 ± 5.1
Current smoking	387 (13.9)	346 (12.4)	406 (14.6)	411 (14.8)

Data are means ± SD, *n* (%), or median (interquartile range).

Joint effects of routine blood pressure lowering and intensive glucose control

The HRs for the combination of blood pressure lowering with perindopril-indapamide and intensive glucose control with gliclazide MR and for either active treatment compared with those for placebo and standard glucose control are shown for all clinical outcomes in Table 2. There was no interaction between the effects of routine blood pressure lowering and intensive glucose control for any of the prespecified clinical end points (all $P > 0.1$), indicating that the effects of these two interventions were independent.

A total of 1,799 participants had a major macrovascular or microvascular event during follow-up: 431 (15.5%) in the joint treatment group and 498 (17.9%) in the group that received neither active intervention, a relative risk reduction of 15% (95% CI 3–25%, $P = 0.02$). Compared with neither active intervention, combined treatment reduced the risk of microvascular events by 19% (3–32%, $P = 0.02$) but had no significant

effect on the incidence of macrovascular events (8% [−10 to 23%], $P = 0.35$).

A total of 2,683 participants had a major renal event during follow-up: 590 (21.2%) in the joint treatment group and 777 (27.9%) in the group that received neither active intervention. Compared with neither active intervention, combined treatment reduced the risk of all renal events by 28% (95% CI 19–35%, $P < 0.0001$), which included a 33% reduction in the risk of new or worsening nephropathy (12–50%, $P = 0.005$), a 54% reduction in the risk of new onset of macroalbuminuria (35–68%, $P < 0.0001$), and a 25% reduction in the risk of new onset of microalbuminuria (16–33%, $P < 0.001$). The effects of each intervention on all renal events were intermediate between those of joint treatment and neither active intervention. When considered separately, the effects of the two interventions were additive on the log scale, and the effect of each intervention was not altered by the other treatment (Fig. 1).

A total of 879 participants died dur-

ing follow-up: 198 (7.1%) in the joint treatment group and 240 (8.6%) in the group that received neither active intervention. Compared with those in neither active intervention, those allocated to joint treatment had a significantly lower annual mortality rate (relative risk reduction 18% [95% CI 1–32%], $P = 0.04$) with the effects of the two treatments being independent of each other (Fig. 2).

CONCLUSIONS — The ADVANCE trial has reported the separate beneficial effects of routine blood pressure lowering with perindopril-indapamide and intensive glucose control with a gliclazide MR–based regimen on a range of vascular complications in patients with type 2 diabetes (4,8). In the present analyses we show that the combined effect of both treatments was at least as great as the effect of either treatment alone for all clinical outcomes and appeared to be greater for some. This finding was most clearly apparent where both blood pressure lowering and intensive glucose control had separate significant beneficial effects, as

Table 2—*Joint effects of routine blood pressure lowering and intensive glucose control on all clinical outcomes*

	Randomized treatments				
	Intensive glucose and perindopril-indapamide	Standard glucose and perindopril-indapamide	Intensive glucose and placebo	Standard glucose and placebo	$P_{\text{interaction}}$
n	2,783	2,786	2,788	2,783	
Primary outcomes					
Combined major microvascular and macrovascular events					
No. events	431	430	440	498	
HR (95% CI)	0.85 (0.75–0.97)	0.85 (0.74–0.96)	0.87 (0.77–0.99)	1.00 (reference)	0.13
Major microvascular events					
No. events	213	226	217	260	
HR (95% CI)	0.81 (0.68–0.97)	0.85 (0.72–1.02)	0.83 (0.69–0.99)	1.00 (reference)	0.32
Major macrovascular events					
No. events	246	234	255	265	
HR (95% CI)	0.92 (0.77–1.10)	0.87 (0.73–1.04)	0.96 (0.81–1.14)	1.00 (reference)	0.44
Other outcomes					
Death from any cause					
No. events	198	210	231	240	
HR (95% CI)	0.82 (0.68–0.99)	0.87 (0.72–1.04)	0.96 (0.80–1.15)	1.00 (reference)	0.90
Death from cardiovascular causes					
No. events	104	107	121	136	
HR (95% CI)	0.76 (0.59–0.98)	0.78 (0.60–1.00)	0.89 (0.70–1.14)	1.00 (reference)	0.62
Major coronary heart events					
No. events	133	132	139	155	
HR (95% CI)	0.92 (0.77–1.10)	0.87 (0.73–1.04)	0.90 (0.71–1.13)	1.00 (reference)	0.47
Major cerebrovascular events					
No. events	111	104	111	107	
HR (95% CI)	1.03 (0.79–1.35)	0.96 (0.73–1.26)	1.03 (0.79–1.35)	1.00 (reference)	0.85
All renal events					
No. events	590	630	686	777	
HR (95% CI)	0.72 (0.65–081)	0.77 (0.69–0.85)	0.88 (0.79–0.97)	1.00 (reference)	0.33
New or worsening nephropathy					
No. events	81	100	96	120	
HR (95% CI)	0.67 (0.50–0.88)	0.82 (0.63–1.07)	0.80 (0.61–1.05)	1.00 (reference)	0.93
New or worsening retinopathy					
No. events	147	142	133	153	
HR (95% CI)	0.96 (0.76–1.20)	0.92 (0.73–1.16)	0.86 (0.69–1.09)	1.00 (reference)	0.27
New onset of microalbuminuria					
No. events	525	542	605	673	
HR (95% CI)	0.75 (0.67–0.84)	0.77 (0.68–0.86)	0.90 (0.80–100)	1.00 (reference)	0.29
New onset of macroalbuminuria					
No. events	44	74	73	95	
HR (95% CI)	0.46 (0.32–0.65)	0.77 (0.56–1.04)	0.77 (0.57–1.04)	1.00 (reference)	0.30

was observed for all renal events and the components of new or worsening nephropathy, new onset of microalbuminuria, and new onset of macroalbuminuria (Table 2). Where a separately significant beneficial effect was observed only for blood pressure lowering (as for all-cause mortality and cardiovascular death), the addition of intensive glucose control did not negate that effect. In fact, for all-cause mortality (Table 2, Fig. 2) and cardiovascular death (Table 2), the estimates of the effect size for the joint intervention were slightly greater than they were for blood

pressure lowering alone. These findings provide considerable reassurance that the widely used clinical approach of joint management of blood pressure and glucose in patients with type 2 diabetes is both appropriate and effective.

Our findings support and strengthen those of the UKPDS (14) and provide further evidence for the benefits of a multifactorial treatment approach that includes blood pressure lowering and intensive glucose control in patients with type 2 diabetes. The previously reported benefits of multifactorial risk management in

the STENO 2 study were obtained through a combination of optimal blood pressure, glucose control, lipid modification, and antiplatelet therapy, although only 20% of participants achieved A1C levels of <7% (11). Our data show that intensification of glycemic control to achieve A1C levels of ≤6.5% augments the benefits obtained with blood pressure–lowering treatment, particularly with respect to renal events. Our study also shows that such an approach has benefits not only for individuals with type 2 diabetes who also have hypertension
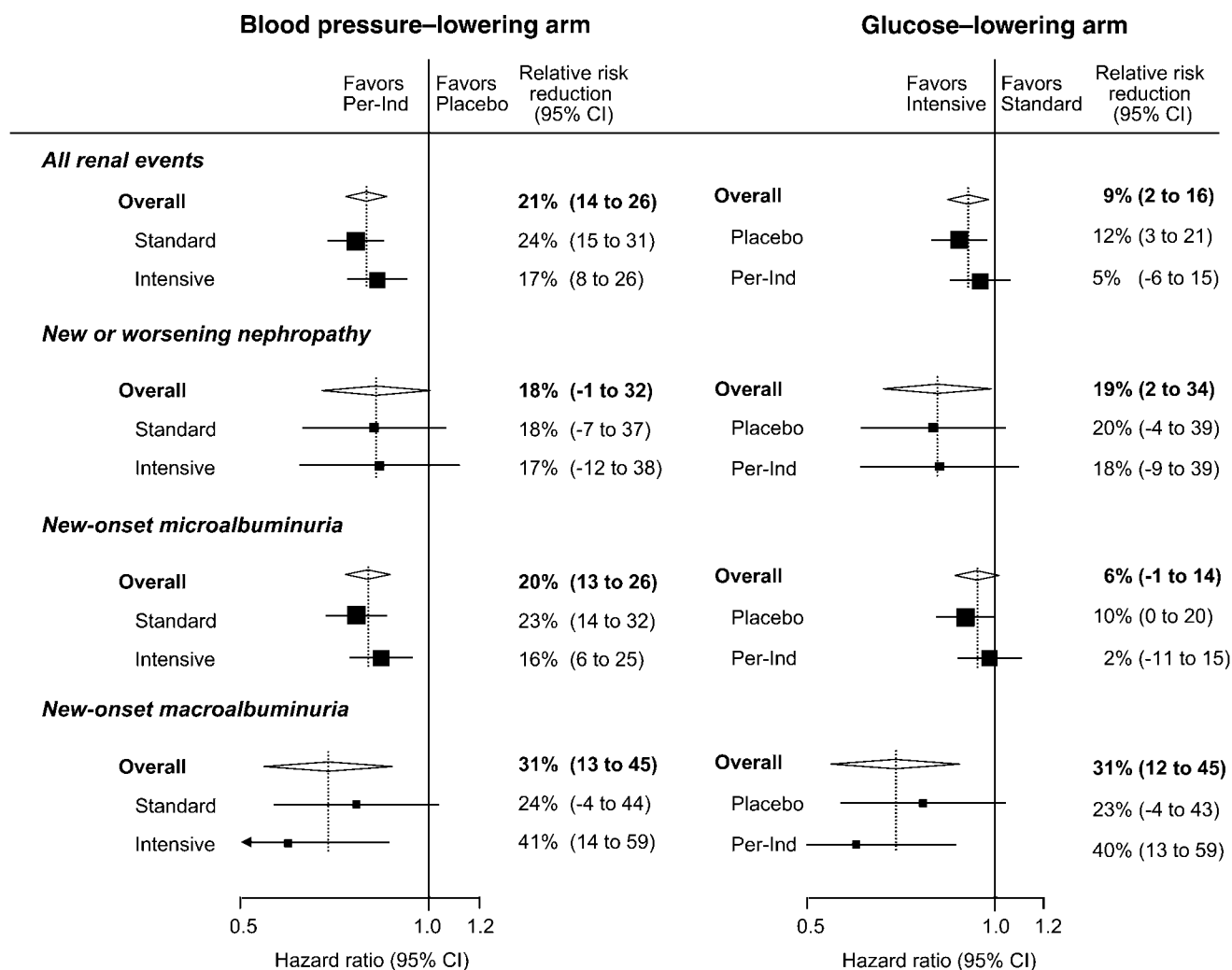
Figure 1—*Relative effects of routine blood pressure–lowering and intensive glucose control strategy on all prespecified renal events. The effects of treatment (HRs) were estimated from unadjusted Cox proportional hazards models that used all available data at 4.3 years of follow-up. The diamonds incorporate the point estimates, represented by the vertical dashed lines, and the 95% CIs of the overall effects within categories; for subcategories, black squares represent point estimates (with the area of each square proportional to the inverse variance of each estimate), and horizontal lines represent 95% CIs. The HRs and relative risk reductions are given for intensive glucose control compared with standard glucose control in the blood pressure–lowering arm and for perindopril-indapamide (Per-Ind) compared with placebo in the glucose-lowering arm.*

(14) or microalbuminuria (11) but for a much broader cross-section of the population with type 2 diabetes.

The substantial renal benefits observed in both arms of the ADVANCE trial and magnified in the group receiving both interventions may also translate into future cardiovascular benefits. Elevated levels of albuminuria have clearly been demonstrated to be a risk factor for cardiovascular disease in patients with type 2 diabetes (17), with current screening strategies aimed to identify affected patients so that appropriate preventive treatments may be introduced. Recent studies have suggested that treatment of albuminuria per se may reduce cardiovascular events (18). Long-term follow-up of the UKPDS study (19) has also demonstrated

that the cardiovascular and mortality benefits of intensive glucose control emerge over time. The combined treatment strategy used in ADVANCE would therefore be anticipated to further reduce cardiovascular risk in the long term.

In the ACCORD study, intensive glucose control increased the risk of death (9). However, the overall mortality rate was much lower than predicted, probably as a consequence of the factorial study design that included intensive blood pressure– and lipid-lowering interventions. Our analyses provide no evidence of such an increase in mortality either in the glucose-lowering arm of the ADVANCE trial as reported previously (8) or in the present analyses. On the contrary, the combination of both active interventions

compared with neither active intervention significantly reduced the risk of all-cause and cardiovascular mortality. There was also no indication that the benefits of routine blood pressure lowering were offset by the intensive glucose control intervention. If anything, the magnitude of risk reduction was somewhat greater in the group receiving both interventions than that observed in the group receiving routine blood pressure lowering alone. It is noteworthy that the intensive glucose control strategies applied in ADVANCE and in ACCORD differed substantially in the way the glucose target was achieved (8,9). Our results indicate that intensive glucose control can be implemented safely through a conventional approach, using the gliclazide MR–based regimen

Death from any cause
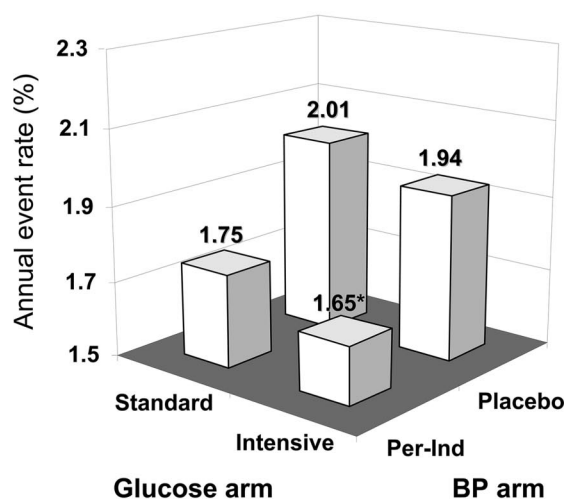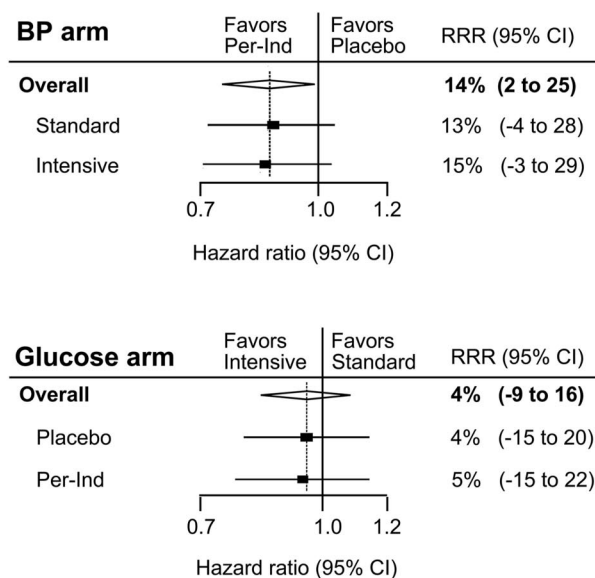
Figure 2—*Combined effects of routine blood pressure–lowering and intensive glucose control strategy on the incidence of death from any cause. Incidence of death from any cause is presented as the annual event rate (percent) by the four randomized treatment groups: intensive glucose control and perindopril-indapamide (Per-Ind), standard glucose control and perindopril-indapamide, intensive glucose control and placebo, and standard glucose control and placebo. The effects of treatment (HRs and P values) were estimated from unadjusted Cox proportional hazards models that used all available data at 4.3 years of follow-up. The diamond incorporates the point estimate, represented by the vertical dashed line and the 95% CI of the overall effect. The HRs and relative risk reductions (RRRs) are given for intensive glucose control compared with standard glucose control in the blood pressure (BP)-lowering arm and for perindopril-indapamide compared with placebo in the glucose-lowering arm.*

and stepwise increase in oral agents and, eventually, basal insulin (8).

Although we found no evidence for an interaction between the blood pressure– and glucose-lowering interventions for any of the outcomes, we are unable to fully exclude the presence of an interaction, particularly for some of the less common outcomes. Exclusion of any interaction between the two interventions of the ADVANCE trial would have required a sample size 4 times as large to be adequately powered (20). The absence of an interaction is further supported by observational data demonstrating that associations of blood pressure levels and measures of glycemic control with the risks of mortality and coronary heart disease in patients with type 2 diabetes are independent and additive (14,21,22).

When the treatments were not demonstrated to have separate significant benefits, as for macrovascular events, such effects were also not observed with combined treatment. One possible explanation is the relatively short length of study follow-up. This may particularly influence the effect of the glucose-lowering strategy for which the rate of macrovascular events only began to diverge in the last 12 months of the average 5-year period of

follow-up, whereas the present analyses were limited to 4.3 years of follow up (8). The resultant loss of a large number of events that occurred with prolongation of the randomized glucose intervention therefore limited the statistical power to detect significant effects. In addition, the lower-than-anticipated event rates, possibly reflecting the comprehensive background management of cardiovascular risk in both arms (4,8), and less-than-projected separation in A1C between the glucose treatment groups may have further reduced the ability to detect an effect reliably. The recent report from the 10-year post-trial follow-up of the UKPDS cohort of significant long-term benefits observed with intensive glucose control for macrovascular events (19) suggests that the ADVANCE trial may have required much longer follow-up to demonstrate clear benefits of intensive glucose (8) or combined treatment for this outcome.

In summary, the ADVANCE trial has demonstrated that a combined approach of routine blood pressure lowering and intensive glucose control resulted in substantial reductions in major renal events and all-cause death. For the major renal outcomes, the separately significant beneficial effects of the two interventions

were additive. This suggests that the multifactorial management of type 2 diabetes should incorporate routine blood pressure lowering and more intensive glucose control to reduce the burden of adverse clinical sequelae in individuals with established diabetes.

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